

**FINAL EVALUATION OF THE  
CONTRACEPTIVE RESEARCH  
AND DEVELOPMENT PROGRAM (CONRAD)  
(936-3044)**

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# TABLE OF CONTENTS

ABBREVIATIONS.....	v
EXECUTIVE SUMMARY .....	vii
SUMMARY OF REDOMMENDATIONS .....	xi
1 BACKGROUND.....	1
1.1 History of CONRAD .....	1
1.1.1 PARFR/ Mandate for CONRAD.....	1
1.1.2 1989 Midterm Evaluation.....	1
1.2 1995 Evaluation Assignment .....	2
1.2.1 Objectives for the 1995 Evaluation.....	2
1.2.2 Contraceptive Research in 1995: the Role of USAID .....	2
1.2.3 Evaluation Team .....	3
1.2.4 Evaluation Schedule.....	4
2 RESEARCH PORTFOLIO .....	5
2.1 Overview .....	5
2.2 Research in Contraceptive Development.....	5
2.2.1 Intramural/Extramural Balance .....	5
2.2.2 Long, Medium, Short-Term Balance.....	7
2.2.3 Specific Contraceptive Leads.....	8
2.2.4 Appropriateness to LDC Needs.....	12
2.3 HIV/AIDS Research .....	13
2.3.1 Mechanisms of Heterosexual Transmission .....	13
2.3.2 The Screening of Spermicidal and Microbicidal Candidates.....	14
2.3.3 Epidemiological and Behavioral Factors Affecting Transmission of HIV/STD's .....	15
3 COLLABORATION AND COOPERATION .....	17
3.1 Overview .....	17
3.2 Programmatic Collaborations with other CAs.....	17
3.3 Collaboration with LDC Institutions .....	17
3.4 Impact of the NIH and CDC Contracts on CONRAD's Contraceptive Research .....	18

4 MISSION AND PLANNING .....	19
4.1 Strategic Planning.....	19
4.1.1 Role of USAID .....	19
4.1.2 Role of the TAC.....	19
4.2 Solicitation of Research .....	20
4.3 Selection of Projects .....	21
4.3.1 Selection of Extramural Projects .....	21
4.3.2 Selection of Intramural Projects.....	21
4.4 Monitoring of Projects .....	22
4.4.1 Project Reporting to CONRAD .....	22
4.4.2 Multi-center Trials .....	22
4.4.3 Reporting to USAID .....	22
5 TECHNICAL ADVISORY COMMITTEE .....	25
5.1 Composition .....	25
5.2 Mandate.....	25
6 FINANCIAL MANAGEMENT.....	27
6.1 Budgeting.....	27
6.2 Financial Reporting .....	27
7 STAFFING, ORGANIZATION AND MANAGEMENT .....	29
7.1 Staffing .....	29
7.2 Organization and Management.....	29
8 FACILITIES .....	31
9 FUTURE DIRECTIONS AND RECOMMENDATIONS .....	33
9.1 Continuation.....	33
9.2 Improved Mechanisms for Policy and Planning .....	33
9.3 Ensuring Program Responsiveness to LDC Needs .....	34
9.4 Relaxing the Product Development Mandate.....	34
9.5 Streamlining and Focusing the HIV/AIDS Portfolio .....	34
9.6 Priorities in the Event of Reduced Funding.....	34

## **LIST OF APPENDICES**

Appendix A	Evaluation Scope of Work
Appendix B	List of Persons Contacted
Appendix C	Bibliography
Appendix D	Chart 1: CONRAD Total Obligations/USAID Funds
Appendix E	Chart 2: CONRAD Total Obligations/USAID/NIH/CDC Funds
Appendix F	Chart 3: CONRAD Table of Organization



## ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
AZT	3'-azido-3'-deoxythymidine (zidovudine)
BZK	benzalkonium chloride
CA	cooperating agency
CDB	Contraceptive Development Branch (NICHD)
CONRAD	Contraceptive Research and Development Program
CPR	Center for Population Research (NICHD)
CTO	cognizant technical officer
DBT	Department of Biotechnology, Ministry of Science and Technology, Government of India
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
FHI	Family Health International
GnRH	gonadotropin releasing hormone
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HRP	Special Programme for Research, Development and Research Training in Human Reproduction (WHO)
ICMER	Instituto Chileno de Medicina Reproductiva
ICMR	Indian Council for Medical Research
IND	investigational new drug application
INNSZ	Instituto Nacional de la Nutricion Salvador Zubiran
IPR	Institute for Primate Research, Nairobi, Kenya
IUD	intrauterine contraceptive device
IVR	intravaginal ring
LDC	less developed country
LNG	levonorgestrel
N-9	nonoxynol-9
NICHD	National Institute of Child Health and Development
NIH	National Institutes of Health
PARFR	Program for Applied Research on Fertility Regulation
PCR	polymerase chain reaction
PI	principal investigator
R&D	research and development
RFA	request for applications
RIHES	Research Institute for Health Sciences, Chiang Mai University
RNA	ribonucleic acid
RTI	reproductive tract infection
SIV	simian immunodeficiency virus
SRI	Southern Research Institute
STD	sexually transmitted disease
TAC	technical advisory committee
TE	testosterone enanthate
TOPCAD	Topical Prevention of Conception and Disease

VCF<sup>R</sup>  
WHO

vaginal contraceptive film  
World Health Organization



# EXECUTIVE SUMMARY

## Background

The CONRAD program is operated under a second five-year cooperative agreement between the US Agency for International Development (USAID) and the Eastern Virginia Medical School (EVMS). Since its inception, the mission of the CONRAD program has been to develop new and improved methods of contraception for use in developing countries. The program was designed to bring promising, near-term leads from the basic research sector into Phase I and II clinical trials. In the first few years of the program, the mandate was expanded to include research on mechanisms of heterosexual HIV/AIDS transmission, epidemiological and behavioral factors affecting transmission, and development of methods to reduce transmission of HIV/STDs.

A 1989 midterm evaluation of CONRAD indicated the program had gotten off-track by over-emphasizing intramural, basic research and had few near-term leads. The program was encouraged to increase the level of extramural funding, limit intramural spending to no more than one-third of the total budget, shift priorities to short-term leads, and better utilize the intramural Clinical Research Unit (CRU).

## Current Strengths

CONRAD has successfully responded to the recommendations made in 1989. Under the leadership of Dr Gabelnick there has been a substantial increase in funding for extramural projects, intramural basic research has been scaled back, and priority has been given to proposals offering near-term leads. The program's effectiveness is enhanced by its relatively small size, the commitment and high quality of its director and professional staff in Rosslyn, and the excellent service provided by the Norfolk CRU. CONRAD has effective systems in place for coordinating activities with other USAID CAs, as well as other US-based, international, and LDC institutions.

New Contraceptive Products. CONRAD will soon have brought three new barrier methods to the contraceptive market. It also has produced promising leads in methods for lactating women, a new vaginal film product (BZK), and some promise for male methods. An important achievement has been the intramural development of tests for spermicidal agents and support of the Southern Research Institute (SRI) for virucidal screening. The recently funded TOPCAD project should bring improved coordination to the screening program, and add screening for anti-gonococcal and chlamydial activity.

Improved Understanding of HIV/AIDS. The addition of HIV/AIDS research appears to be complementary to the contraceptive research program. CONRAD's successful development of a simian model for heterosexual transmission and its contributions to current understanding of the physiology of HIV infection in the human genital tract provide important avenues for better evaluating the impact of contraceptive methods on disease transmission.

Collaboration. CONRAD is to be commended for the excellent job it has done in communicating and collaborating with other agencies, including CDC, FDA, FHI, HRP/WHO, Mellon, NIH, and the Population Council. CONRAD's collaborative activities have elicited consistent high praise.

## **Areas for Improvement**

Policy and Planning. It is strongly recommended that CONRAD establish a small strategic planning entity or "policy unit", to ensure development of long-term strategic plans, oversight for TAC appointments, and annual review of the program. Such a unit is critical if CONRAD is to further develop its institutional visibility, and further expand its funding base. CONRAD's management can be improved in several other areas, and a management consultant should be contracted to assist CONRAD in this regard.

Appropriateness for Developing Countries. Better and clearer mechanisms should be established to ensure CONRAD's responsiveness to LDC needs. LDC appropriateness of individual product leads should be adequately addressed from the early stages of product development. LDC participation in the TAC is strongly recommended, as is LDC representation in the recommended "policy unit". Many LDC institutions are working in this area, from which CONRAD advisors can be drawn.

Relaxing the Product Orientation. The USAID mandate for rapid product development should be relaxed, allowing increased opportunities for exploration of long-term leads. The current mandate may be narrowing the likelihood of achieving the overall objective of developing new and improved contraceptive methods for LDCs. A significant portion of the portfolio has been directed to the development of female-controlled barrier methods. While such methods will likely be welcomed by many women (especially if they do not require fitting and/or can be used without spermicide), the relatively high pregnancy rates associated with these methods is reason for concern; access to safe abortion is still very limited in many developing countries. Without disregarding female-controlled, self-fitting, mechanical and chemical barriers which also protect against disease, the program should be provided ample flexibility to explore long-term leads for provider-dependent, long-acting, coital-independent methods, including methods to be used by men.

Streamlining and Focusing the HIV/AIDS Portfolio. There is a need for CONRAD to develop a strategic, coordinated plan for rapid advancement of products through toxicology, to evaluations in the simian model, and to human testing. While the epidemiologic and behavioral HIV research funded by CDC provides some intellectual complementarity to CONRAD's interests, it is not optimally suited to CONRAD's mission and technical expertise; epidemiologic and social science projects of this nature may be better handled by another agency. On the other hand, the CONRAD intramural capacity to carry out pharmacokinetics studies could be better used to investigate interactions between systemic contraceptive agents and anti-HIV drugs.

## **The Future**

The CONRAD program is making important contributions to the field of fertility regulation and reproductive health. Given the strengths and commitment of its director and professional staff,

manifest in recent accomplishments in both product development and fundamental HIV research, the evaluation team strongly recommends that the CONRAD program be continued for an additional ten years, with appropriate review after five years. The evaluation team sees no advantages in merging CONRAD with any of the other USAID CAs, and recommends that the continuation of CONRAD not be competed.

The team's major recommendations are directed to further improving CONRAD's effectiveness. Establishment of a "policy unit" will help CONRAD keep track of pivotal innovations in basic research, and guide the program selection of long-term and short-term investments. A management expert can help develop systems for increasing CONRAD's internal efficiency, and increasing its visibility domestically and internationally. CONRAD's responsiveness to current and future LDC needs can be increased by building avenues for greater LDC participation and input at all levels of the program. Finally, a relaxation of USAID's mandate for rapid product development is encouraged, in order to provide CONRAD the necessary flexibility to invest in long-term and medium-term leads in important areas. If attention is given to these and other recommendations posed in this report, the team expects CONRAD to increase its already considerable contributions to the field of population and reproductive health.



## SUMMARY OF RECOMMENDATIONS

1. Attention to female-controlled mechanical barriers should continue only in the event that new methods offer significant improvements over existing products. Such improvements would include increased effectiveness without spermicide, no-fit or easy-fit methods, or methods that could provide barrier protection over the vulva and/or labia. (p. 8)
2. Research on male methods deserves substantial support, but the current emphasis on available hormonal combinations should be complemented by intensified research on more potent and/or long-acting androgens. (p. 10)
3. **Expanded efforts should be devoted to the development of male contraceptive products and delivery systems that have an increased likelihood of acceptability, e.g. long-acting androgen esters that might offer effectiveness over three months, or sustained delivery systems for shorter-acting compounds.** (p. 10)
4. Although the copper wire lead may be discontinued, efforts to identify agents that may act at the epididymal/vas deferens levels should continue. (p. 10)
5. **The immunocontraception program should be reviewed and hard decisions regarding CONRAD's future investment need to be taken. Systematic plans and criteria for current leads should be further developed, and operations at IPR should be assessed. In order to avoid potential conflicts of interest, the review group should include immunologists and product development specialists who do not have a direct professional interest in immunocontraception.** (p. 11)
6. Efforts to develop contraceptive methods for lactating women should proceed at full speed in order to have a product available for postpartum use in LDC countries as soon as possible. ICIMER appears to be an appropriate institution to lead these efforts with CONRAD support. (p. 12)
7. Continuing support for a new sequential anovulatory pill is encouraged. (p. 12)
8. **Without disregarding female-controlled, self-fitting, mechanical and chemical barriers which also protect against disease, the program should give appropriate priority to provider-dependent, long-acting, coital-independent methods, as well as methods to be used by men.** (p. 12)
9. **Better and clearer mechanisms should be established to assure that the appropriateness of products to LDC needs is adequately addressed from the early stages of the contraceptive development process. Such evaluations should ideally take place with a critical mass of LDC advisors, and might be effectively aired through meetings coordinated by the program's LDC collaborative research sites.** (p. 13)

- 10. CONRAD should focus future investment in HIV model studies to investigate the mechanisms by which contraceptive methods may affect HIV transmission and infection. (p. 14)**
11. CONRAD's continuing investment in the simian model of HIV infection should be focused on the effects of contraceptive methods and virucides on SIV infection. (p. 14)
12. CONRAD should review whether Dr Doncel's supervision of the laboratory by fax, telephone and periodic visits is effective, or whether an interim appointment (or other such alternative) would significantly accelerate or improve work in this area. (p. 15)
- 13. CONRAD should prepare a strategic, coordinated plan for rapid advancement of spermicidal/virucidal candidates through toxicity, to evaluations in the simian model, and to human testing. (p. 15)**
- 14. Epidemiologic and behavioral research are not areas where CONRAD possesses the comparative advantages that it has in other areas of research in which it is involved. Either CDC-funding for these projects should provide for additional CONRAD professional staff in epidemiology and/or social science, or CDC-funded projects of this nature may be better handled by another agency. (p. 16)**
15. CONRAD should capitalize on existing developing country centers to increase the level of engagement and participation of LDC scientists (and others) in the CONRAD program. (p. 18)
- 16. There is a strong need for CONRAD to establish a policy unit/entity that would provide "board-like" functions, including the development of long-term strategic plans, oversight of TAC appointments, and annual review of the program. LDC participation in the unit is recommended. (p. 20)**
17. Workshops sponsored by CONRAD should include invitations to professionals who may not currently be engaged in contraceptive research, but who may be encouraged, through participation at the workshop, to develop project proposals investigating contraceptive applications of their work. (p. 21)
- 18. Increased outreach to the international scientific community by professional staff is encouraged. Advertisement in foreign national journals should be explored, and increased efforts should be made to solicit research ideas through existing associations with developing country scientists (e.g. through the Mellon Centers). (p. 21)**
19. Increased institutional presence at professional meetings, and establishing a CONRAD "booth" at large meetings should be considered. (p. 21)
20. The CONRAD brochure should be reviewed and improved by an appropriately qualified consultant. (p. 21)

21. Broader TAC and staff collaboration in generating and developing good proposals from promising ideas (extramural and intramural) should be encouraged. (p. 22)
22. The establishment of clear criteria to judge the appropriateness to LDC needs is encouraged. (p. 22)
23. The experience and closer relations with clients of the Norfolk staff can provide significant input to the program. The director and senior staff at the CRU should be encouraged to participate more actively in generating subprojects, reviewing proposals and developing general strategies for the program. (p. 22)
24. CONRAD should consider the possibility of producing only an annual report to USAID, which would not include detailed project-by-project reviews, but would provide an overarching annual review of CONRAD's progress and a strategic plan of work for the coming year. (p. 23)
25. CONRAD should investigate developing a system of research lead "champions" among staff professionals (and possibly in partnership with individual TAC members), both to increase staff and TAC accountability for given leads, and to accelerate progress on individual lines of research. (p. 23)
26. The TAC mandate should be modified to include review of policy issues brought to it by the "policy unit/entity" described in Recommendation 16. The agenda should be modified to allow time for such policy review. (p. 25)
- 27. There is a clear need to increase representation from developing countries, both in the TAC, and in the recommended "policy unit". (p. 25)**
28. A formal procedure for selection of new TAC members should be established. (p. 25)
29. There is a need to review the issue of term limits, and the evaluation team recommends establishment of three-year (once-renewable) limits for TAC members. (p. 25)
30. USAID should approve CONRAD's plans for modest additions to staff in Rosslyn. (p. 29)
- 31. A management consultant should be contracted to assist CONRAD and USAID to address the management issues identified above. (p. 29)**
32. CONRAD should take better advantage of the capability which exists in Norfolk by, for example, having the chief of the CRU participate in CONRAD staff meetings. (p. 29)
- 33. The CONRAD program should be continued as an independent CA for an additional ten years, with appropriate review at five years. The continuation should not be competed. (p. 33)**





# 1 BACKGROUND

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## 1.1 History of CONRAD

### 1.1.1 PARFR/ Mandate for CONRAD

The Contraceptive Research and Development Program (CONRAD) was created in 1986 to develop new and improved methods of fertility regulation for use in developing countries. CONRAD was a successor to the Program for Applied Research on Fertility Regulation (PARFR), expanded by the addition of intramural research activities.

The CONRAD mandate, since its inception, has been to focus on moving contraceptive leads from the early stages of R & D through clinical research. Thus, highest priority has been accorded to moving potential products through Phase I and II clinical trials. The dedication of approximately one-third of CONRAD's resources to intramural research was judged essential for moving contraceptive leads rapidly from the laboratory to clinical trials.

After CONRAD was initiated, interagency agreements between USAID and the National Institutes of Health (NIH) and the Centers for Disease Control (CDC), led to increased funding for CONRAD to conduct research on HIV/AIDS. The expanded mandate includes research on mechanisms of heterosexual transmission of HIV, screening for agents with both anti-sperm and microbicidal activity, and epidemiologic and behavioral research related to HIV/STDs. Thus, the contributions of NIH and CDC expanded and complemented the initial mandate of CONRAD.

In order to achieve its objectives, CONRAD was designed to incorporate a balance of intramural and extramural research capabilities. The intramural research program, based at Eastern Virginia Medical School (EVMS), has the capacity for basic laboratory work, pre-clinical studies, as well as Phase I and Phase II clinical trials. The extramural CONRAD offices are designed to identify, fund and nurture extramural projects consistent with program objectives. The cooperative agreement suggested that the program will probably achieve highest efficiency by allocating about one third of the financial resources to intramural activities and two thirds to extramural projects.

### 1.1.2 1989 Midterm Evaluation

The 1989 midterm evaluation of CONRAD found that almost half the budget was allocated to intramural research, and a disproportionately high fraction of that research was directed to long-term contraceptive leads at the expense of medium- to short-term leads. The evaluation recommended a restoration of the one-third/two-thirds balance for intramural/extramural research that had been specified in the initial cooperative agreement, and a concerted effort to re-focus the program on near-term leads. It was noted that active solicitation of extramural proposals needed to be increased, and that the intramural Clinical Research Unit (CRU) should be better utilized and expanded.

In response to these recommendations, CONRAD moved the program management to Rosslyn and expanded staff devoted to the management of extramural subprojects. At the same time, it

significantly reduced the basic laboratory research program carried out with intramural funding, and expanded the intramural CRU at EVMS.

A second five-year cooperative agreement was signed in 1992 for the period June 1 1992 through May 31 1997. This new agreement for CONRAD II had several notable changes from the original agreement: acknowledging the program's additional mandate to conduct research on HIV/AIDS, the CA indicates that in addition to conducting research on new methods of fertility regulation, research will also be directed "at better understanding the mechanism of transmission of HIV and other STD pathogens, assessing the impact of contraceptive practices on transmission, and developing contraceptives that reduce transmission". Within the contraceptive research and development portfolio, no more than one-third should be intramural. The emphasis on medium- and short-term leads, and the objective of fulfilling needs of developing countries, continue as cornerstones of the CONRAD mandate.

## **1.2 1995 Evaluation Assignment**

### *1.2.1 Objectives for the 1995 Evaluation*

The purposes of this 1995 evaluation have been to:

- Assess the current strengths and weaknesses of the CONRAD program.
- Determine whether recommendations made during the 1989 midterm evaluation have been adequately addressed.
- Recommend whether or not the CONRAD program should be continued.

*In the event that the evaluation team recommends that CONRAD be continued, the team has been charged to address the following specific questions:*

- Should CONRAD continue as an independent CA, or could it be effectively merged with FHI (or Population Council)?
- Are any aspects of CONRAD's current research portfolio redundant with that of other USAID CAs?
- Should a continuation of the program be competed?
- How can CONRAD be more effective?
- And, finally, in the event of significant reductions in USAID funding, what lines of work should be continued, scaled back, or phased out?

(See Appendix A for the complete scope of work.)

### *1.2.2 Contraceptive Research in 1995: the Role of USAID*

Recent political changes in the US Congress raise the specter of significant reductions in Congressional allocations to USAID in the near future. Given the breadth of USAID programs and

commitments, what is the rationale for continued, or increased funding to contraceptive research and development?

Contraceptive options available today are inadequate to fulfill the expanding global need for contraception. The demand for new, better, and more acceptable products is evident in the numbers of contraceptive users who try, but rapidly discontinue, current methods of contraception. It is also evident in the alarmingly high numbers of unplanned pregnancies (and subsequent abortions) that occur worldwide. The high incidence of abortions in countries where modern contraceptive methods are widely available underscores the fact that a simple expansion of existing contraceptive services throughout the world will be insufficient to address the public need for birth control; new, better methods are needed.

Public need for several specific classes of contraception have been emphasized by public-interest groups: methods that can be used by men, methods for use by breast-feeding women, and methods that also provide protection to men and women against sexually transmitted diseases, including HIV. Each of these methods warrant increased research support.

But more is needed. Most existing contraceptive leads are variations on endocrine-related methods, a class of methods heralded more than 30 years ago. Immunocontraception may represent the only true innovation in contraceptive research in the last 20 years - and regrettably this appears to lack any immediate promise for application. Innovative research is badly needed, and concerted efforts must be made by USAID, through CONRAD, to locate and foster the scientific developments that will provide new technologies for the future.

As other sources of international support for contraceptive research decline, USAID plays an increasingly pivotal role in determining whether reproductive health will improve, or decline, in the 21st century. USAID support to CONRAD, the WHO/HRP, FHI and the Population Council represent critical investments in the future health and welfare of developing countries.

### *1.2.3 Evaluation Team*

The evaluation team included a reproductive biologist, a virologist, an obstetrician and director of a major developing country hospital, and a senior management expert. The team members were:

- Rachel C Snow, ScD, Assistant Professor of Reproductive Health, Department of Population and International Health, Harvard School of Public Health, Boston, MA (team leader)
- Jeanine Buzy, PhD, AAAS Fellow and NGO Coordinator, USAID Global Bureau, HIV-AIDS Division, Washington, DC.
- Anibal Faundes, MD, Full Professor in Obstetrics and Director, Centro de Atencao Integral a Saude da Mulher (CAISM) - UNICAMP, Campinas, Brazil
- Robert Wickham, PhD, Management Consultant, Santa Fe, New Mexico

#### *1.2.4 Evaluation Schedule*

The evaluation took place over two weeks (March 17-28) and included the following:

- Three initial days of briefings by USAID and CONRAD staff in Rosslyn, VA.
- Two days at CONRAD's clinical research facility at Eastern Virginia Medical College, Norfolk VA. This visit included interviews with CONRAD staff in Norfolk, and an initial briefing with the program director.
- A second week devoted to review of documentation, follow-up meetings with CONRAD staff in Rosslyn, and consultations with outsiders including principal investigators of selected sub-contracts (see Appendix B for list of persons interviewed). A second, detailed briefing was held with the program director, and final briefings were held with both USAID and CONRAD professional staff.

## **2 RESEARCH PORTFOLIO**

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### **2.1 Overview**

Consistent with recommendations made in the midterm evaluation, CONRAD has undertaken significant changes in its research portfolio since 1989. The current program includes research focussed on new methods of fertility regulation, methods that may reduce transmission of HIV and other pathogens; research on the mechanisms of HIV transmission; and studies on epidemiologic and behavioral risk factors for HIV/AIDS transmission. The leads being followed correspond to the priorities established in the cooperative agreement, with the single exception being the absence of a subproject addressed to the development of non-surgical and/or reversible sterilization for men or women.

The areas of research, the number of subprojects and the budget allocated by area are shown in Table 1. Approximately 53 percent of the budget for extramural subprojects is allocated to contraceptive development and almost 46 percent to HIV/STDs research subprojects. The budget for intramural projects is a small fraction of the total, but it does not include salaries of the EVMS/Norfolk staff.

### **2.2 Research in Contraceptive Development**

Numerous leads for development of new or improved contraceptives are being followed: mechanical and chemical barrier methods, immunocontraception, systemic and local male methods, methods for lactating women and a new concept in oral contraception. The possibility of using new delivery systems are explored across these various leads.

Within the contraceptive development subprojects, one third of the budget went to immunocontraception, 24 percent to systemic male, 19 percent to mechanical and 12 percent to chemical barriers. Subprojects on hormonal female methods, contraception for lactating women, local male methods and sterilization received minimal proportions of the budget (see Table 1).

#### *2.2.1 Intramural/Extramural Balance*

Consistent with 1989 recommendations, there has been a clear increase in funding for extramural projects while intramural spending has been reduced. This was done by cutting out most of the intramural pre-clinical, laboratory work, which is presently limited to in-vitro testing of potential spermicidal substances, and the development of new tests of sperm fertilizing capacity. Intramural clinical research receives a small portion of total funds obligated at present, but several new clinical projects are anticipated. The number of extramural subprojects has increased considerably. However, there is still space for expanding the active solicitation of proposals, particularly from developing countries.

TABLE 1

EXTRAMURAL PROJECTS  
Effective as of April 1995

### 2.2.2 Long, Medium, Short-Term Balance

The CONRAD contraceptive portfolio can also be classified by specific leads, and whether such leads are likely to take a long, medium, or short time before bringing a product to Phase III clinical trials. Table 2 shows the number of current subprojects devoted to long, medium and short-term leads, and Table 3 indicates the current budget allocations to each category.

TABLE 2

<b>LONG, MEDIUM AND SHORT TERM CONTRACEPTIVE LEADS: NUMBERS OF PROJECTS Effective as of April 1995</b>				
TYPE OF METHOD	LONG	MEDIUM	SHORT	TOTAL
Mechanical Barriers	0	2	3	5
Chemical Barriers	2	3	1	6
Systemic Male	3	3	0	6
Local Male	1	1	0	2
Immunocontraception	5	0	0	5
Lactating Women	1	0	2	3
Oral Anovulatory	0	1	0	1
<b>TOTAL</b>	<b>12</b>	<b>10</b>	<b>6</b>	<b>28</b>

TABLE 3

<b>LONG, MEDIUM AND SHORT TERM CONTRACEPTIVE LEADS: CURRENT ALLOCATIONS* Effective as of April 1995</b>				
TYPE OF METHOD	LONG	MEDIUM	SHORT	TOTAL
Mechanical Barriers	0	388,459	1,683,094	2,071,553
Chemical Barriers	388,567	NA**	15,000	403,567**
Systemic Male	747,993	1,136,398	0	1,884,391
Local Male	25,000	275,390	0	300,390
Immunocontraception	1,618,768	0	0	1,618,768
Lactating Women	176,654	0	102,551	279,205
Oral Anovulatory	0	82,946	0	82,946
<b>TOTAL</b>	<b>2,932,007</b>	<b>1,883,193</b>	<b>1,800,645</b>	<b>6,640,820</b>

\* Allocations do not include intramural salaries, and therefore allocations for leads currently undergoing short-term intramural clinical testing (e.g. Allandale film plus BZK or N9) - likely under-estimate total costs to CONRAD.

\*\* Three (3) compounds have passed spermicidal and microbicidal screening, and are about to undergo vaginal irritation studies.

CONRAD's attention to near-term leads has resulted in two methods passing Phase II and III clinical trials (Lea's Shield and the Reality female condom), which led to marketing approval for the Reality

condom. An additional method is currently in Phase II/III clinical trials (FEMCAP).<sup>(\*)</sup> Of a total of 28 contraceptive leads, 12 are long-term, ten can be classified as medium-term and six are short-term leads. All of the long term leads are mission-oriented studies, applied to the development of new methods of fertility regulation (Table 2).

### *2.2.3 Specific Contraceptive Leads*

CONRAD had funded subprojects for the development of five mechanical barrier methods; six leads for new chemical barriers (in addition to their program for spermicidal/virucidal screening); five leads in immunocontraception; six leads for systemic male methods; two leads for a local male method; three potential methods for lactating women; and one oral anovulatory sequential pill using a combination of anti-progesterone with a progestogen.

Mechanical Barriers. CONRAD has been successful in pushing the development forward of three barrier methods that have already passed (or are currently in) Phase II/III clinical trials: the Reality female condom, Femcap, and Lea's Shield. Two additional new female barrier methods are being studied: a disposable vaginal polyurethane sponge composed of two sections held together by a chemical product that will serve as a barrier as well as adhesive layer; and an "easy-fit" silicone diaphragm to be developed at PATH. The first sponge prototypes will soon be ready for a Phase I fitting trial to be conducted at EVMS, and clinical testing of a prototype of the new diaphragm is expected to begin by the end of 1995. The purpose of development in this area is to provide new female-controlled methods that will not require provider intervention and will also contribute to disease prevention.

### **Recommendation**

1. Attention to female-controlled mechanical barriers should continue only in the event that new methods offer significant improvements over existing products. Such improvements would include increased effectiveness without spermicide, no-fit or easy-fit methods, or methods that could provide barrier protection over the vulva and/or labia.

Chemical Barriers. This is an area in which CONRAD has dedicated special efforts and has funded a relatively large number of subprojects. The studies being funded range from synthesis of new compounds which offer some promise of spermicidal and/or virucidal effect, to clinical evaluation of the effectiveness and side effects of different vehicles for releasing nonoxynol-9 in the vagina. An important achievement in this area has been the intramural development of laboratory tests at EVMS for in-vitro evaluation of potential new products for their effects on sperm function. CONRAD has also supported an extramural subproject at the Southern Research Institute (SRI), to carry out testing of the virucidal activity of the same agents. These two laboratories have been used to test different dose regimens of more than 200 substances received from a wide variety of sources. Three compounds have been selected for rabbit vaginal irritation studies. The workplan on positive leads is to carry out contraceptive efficacy studies in animals (rabbits), followed by Phase I spermicidal studies, after FDA approval of the INDs.



Experience gained in this area led to the evaluation and funding of a project (Topical Prevention of Conception and Disease, TOPCAD), that will test a number of different substances with potential for topical contraceptive and disease prevention effects. The TOPCAD project will capitalize on the EVMS and SRI screening capabilities, but has the merit of coordinating (with CONRAD input), each step of testing, up to and including clinical and acceptability studies. The TOPCAD project will also screen prospective agents for anti-gonococcal and anti-chlamydia effects.

Independent of the two screening programs described above, another subproject is investigating the development of hemicholinium lipids with spermicidal and viricidal activity. A fourth, medium-term subproject will evaluate the spermicidal efficacy of an acrosin inhibitor, but has experienced numerous delays due to formulation and stability problems of the suppositories prepared for Phase I testing.

Finally, two subprojects are following a short-term lead--testing a new type of vaginal film (Allendale Film\*) that can be impregnated with available spermicide, and offers the potential advantages of being more stable, quicker to dissolve, and possibly less expensive than the commercially available Vaginal Contraceptive Film (VCF)\*. The spermicidal efficacy of the Allendale Films impregnated with 100 or 130 mg of nonoxynol-9, or with 19 or 25 mg of benzalkonium chloride has been compared with that of the commercially available Vaginal Contraceptive Film (VCF®) (two doses of nonoxynol-9, 100 and 130 mg, were tested against the 72 mg N-9 VCF®). All models showed marked spermicidal activities, without significant differences between them. These studies were carried at the CONRAD CRU at EVMS.

Systemic Male Methods. CONRAD has funded several subprojects on hormonal male contraception and one subproject that explores a long-term lead of non-steroidal agents (ketaconazole-related compounds) and has collaborated with the South to South Cooperation in Reproductive Health in the study of gossypol.

In hormonal contraception, CONRAD has provided funding to two centers (University of Washington and Harbor-UCLA Medical Center) participating in a multi-center study coordinated by the WHO Task Force on Methods for the Regulation of Male Fertility. The study is a Phase II efficacy trial of 200 mg testosterone enanthate (TE) delivered by weekly intramuscular injection; efficacy is only evaluated among men who achieve  $\leq 3 \times 10^6$  sperm/ml. While it is recognized that a weekly injectable is not feasible, the study was designed as a prototype to investigate which level of oligospermia was sufficient to produce a consistent contraceptive effect. Results to date indicate that severe oligospermia (less than  $3 \times 10^6$  sperm/ml) is associated with a low risk of pregnancy.

Another subproject studied a combination of a daily pill of 500 mcg levonorgestrel (LNG), with a weekly intramuscular injection of 100 mg of TE; this was compared against TE alone. Oligospermia was achieved faster by more men with the combination than with TE alone, but high density lipoprotein (HDL) levels were 23 percent lower among men treated with the combined product. Evaluation of the HDL effects is critical to the development of systemic steroid methods for men. Current studies are evaluating lower doses of LNG, and evaluating desogestrel as an alternative progestogen in the same type of combined progestogen/androgen regimen.

CONRAD recognizes that the currently available leads have a low chance of widespread acceptability, as they require frequent injections of large amounts of steroid. More effort should be

spent looking at longer-acting androgens (which could be given less frequently), and more potent androgens (which could be given in lower doses), and evaluating these alone, or in combination with long-acting progestagens. Work should be focused on products that hold promise for widespread acceptability, e.g. long-acting androgen and gestagen esters that might offer effectiveness over three months, or sustained delivery systems for shorter-acting compounds.

CONRAD continues to support research on a combined GnRH antagonist and replacement testosterone ester, by evaluating a regimen that would require only a priming dose of antagonist. Recognizing that costs of current leads may be prohibitive, CONRAD is appropriately shifting research from peptide to a search for non-peptide analogs of GnRH.

In collaboration with the South-to-South Program in Reproductive Health, CONRAD is supporting gossypol assays at Cornell Medical College in blood samples from men participating in non-CONRAD funded clinical trials of the drug. The objective is to evaluate the possible association between gossypol plasma levels and hypokalemia, and reversibility of sperm suppression.

## **Recommendations**

2. Research on male methods deserves substantial support, but the current emphasis on available hormonal combinations should be complemented by intensified research on more potent and/or long-acting androgens.
3. **Expanded efforts should be devoted to the development of male contraceptive products and delivery systems that have an increased likelihood of acceptability, e.g. long-acting androgen esters that might offer effectiveness over three months, or sustained delivery systems for shorter-acting compounds.**

Local Male Methods. Studies on the effect of increased scrotal temperature on sperm production in normal males have induced only a small increase in temperature (1°C or less) with no effect on sperm count. A study of the spermicidal effect of copper wire in the vas deferens demonstrated a decrease in sperm motility over that among controls; the effect was not significantly different from that observed with stainless steel. Further studies (and ideas) are needed to push this lead forward.

## **Recommendation**

4. Although the copper wire lead may be discontinued, efforts to identify agents that may act at the epididymal/vas deferens levels should continue.

Immunocontraception. Three subprojects have explored the antigenicity and/or anti-fertility effect of sperm antigens and two subprojects have studied zona pellucida antigens. Progress has been slow, and no lead is near Phase I clinical trials.

CONRAD has also supported the Institute of Primate Research (IPR) in Nairobi, Kenya, for the evaluation of promising prototype vaccines at relatively low cost. Non-human primate testing to date has validated, in part, the principal of immunocontraception, but more work will be needed on concomitant immunogens, immunogen design, clinically acceptable adjuvants, and vaccine delivery systems. There are conflicting views regarding the pace of CONRAD's (and NIH's) immunocontraceptive research to date: some expressed frustration that there has been too much encouragement to get to primate testing before the prototype vaccines were ready; others stated that projects have remained for too long in the molecular biology phase, and there has been excessive reluctance to move to animal testing of selected antigens. These views suggest that more systematic planning of the sequence of research, with greater orientation to product development, may be warranted.

Concerns were raised regarding operations at the Institute of Primate Research.

The Vaccine Working Group met in March to review the merits of present projects and future priorities, as well as the level at which CONRAD should support immunocontraception studies. The working group developed a strategy and criteria for selecting leads to be pursued further.

## **Recommendation**

- 5. The immunocontraception program should be reviewed and hard decisions regarding CONRAD's future investment need to be taken. Systematic plans and criteria for current leads should be further developed, and operations at IPR should be assessed. In order to avoid potential conflicts of interest, the review group should include immunologists and product development specialists who do not have a direct professional interest in immunocontraception.**

Methods for Lactating Women. CONRAD is supporting the Instituto Chileno de Medicina Reproductiva (ICMER) in Santiago, Chile, an institution that has been a leader in this area. The subproject includes setting up manufacture of progesterone vaginal rings, testing their pharmacokinetic profile and carrying out Phase II clinical trials comparing the new ring with IUDs in lactating women. Enrollment in the study is complete. Preliminary data indicate that rings manufactured in Chile do not provide the expected rate of release, and manufacturing will need re-evaluation.

Other forms of progesterone administration during lactation are being explored. One is a pharmacokinetic study of daily administration of 200 mg progesterone vaginal suppositories, carried out and completed at ICIMER and at the CONRAD CRU at EVMS. Another is an injectable with progesterone monolithic microspheres, to be manufactured in Mexico and in Massachusetts. The Mexico study has been delayed by a series of problems, presently being solved.

## Recommendation

6. Efforts to develop contraceptive methods for lactating women should proceed at full speed in order to have a product available for postpartum use in LDC countries as soon as possible. ICIMER appears to be an appropriate institution to lead these efforts with CONRAD support.

New Sequential Anovulatory Pill. An innovative approach to oral contraception is being tested. It is a sequential pill that may effectively inhibit ovulation by administration of anti-progestins in the first part of the cycle and a progestogen in the second half, as replacement therapy.

## Recommendation

7. Continuing support for a new sequential anovulatory pill is encouraged.

### *2.2.4 Appropriateness to LDC Needs*

One concern that should be more carefully addressed within CONRAD is the appropriateness of current contraceptive leads to developing countries needs. The development of women-controlled methods that do not require fitting and/or can be used without spermicide, will be welcomed; such methods have the potential to be used by a much larger proportion of women than the small number presently using the diaphragm or cervical cap. However, the relatively high pregnancy rate associated with these methods is reason for concern, given that access to legal or safe abortion is limited in many developing countries, excluding China.

The evaluation team recognizes that "appropriateness to developing countries needs" is difficult to define, and that a wide range of needs must be met: from user-controlled, coital-related methods to provider-dependent, long-acting, and coital-independent methods. Given the difficulties in defining market "appropriateness" for LDC countries, it is critical that CONRAD make use of multiple sources of advice and consultation regarding LDC market needs and preferences. As echoed in later recommendations throughout this report, CONRAD is encouraged to increase participation by LDC nationals in program planning.

## Recommendation

8. **Without disregarding female-controlled, self-fitting, mechanical and chemical barriers which also protect against disease, the program should give appropriate priority to provider-dependent, long-acting, coital-independent methods, as well as methods to be used by men.**

In this regard, it is encouraging to note that when a generic Norplant becomes available, CONRAD intends to initiate studies to validate its safety and effectiveness, so as to make it available at a price compatible with developing countries' economies.

## **Recommendation**

- 9. Better and clearer mechanisms should be established to assure that the appropriateness of products to LDC needs is adequately addressed from the early stages of the contraceptive development process. Such evaluations should ideally take place with a critical mass of LDC advisors, and might be effectively aired through meetings coordinated by the program's LDC collaborative research sites.**

## **2.3 HIV/AIDS Research**

The HIV/AIDS epidemic has highlighted public need for greater understanding of the interrelationship between fertility regulation and sexually transmitted disease (STD) management, including the many biological, behavioral and sociological factors affecting human sexual practice, use of contraception, and the effectiveness of existing protective technologies. CONRAD has several activities which address these important and complex issues. In cooperation with NICHD and CDC, CONRAD is funding HIV/AIDS-related research in three broad programmatic areas: the mechanisms of heterosexual transmission of HIV; the screening of spermicidal and microbicidal agents; and the epidemiologic and behavioral risk factors for HIV and STD transmission. The evaluation team has been asked to assess the strengths and weaknesses of the HIV/AIDS portfolio, as well as the effect which the NICHD and CDC contracts have on the overall contraceptive development program.

### *2.3.1 Mechanisms of Heterosexual Transmission*

Localization of HIV. CONRAD/NICHD has funded several successful histological studies identifying the localization of HIV in the urogenital tracts of men and women. These research efforts have contributed important findings, including that 1) HIV RNA and DNA are not detected in viable sperm; and 2) the endocervix may have increased susceptibility to HIV infection, compared to the vagina, exocervix and endometrium. CONRAD funding provided critical transitional support for this research, which now receives additional other sources of funding. By increasing present understanding of the basic biology of heterosexual HIV transmission, this research laid the ground work for identifying potential avenues for new disease-prevention technologies.

Currently, CONRAD is funding a study using in-situ PCR to detect the localization of latently infected cells of the lower genital tracts of men and women, and to detect possible co-factors of infection in the reproductive tract, including inflammation and some effects of contraception.

## Recommendation

10. **CONRAD should focus future investment in HIV model studies to investigate the mechanisms by which contraceptive methods may affect HIV transmission and infection.**

Models of HIV Infection. CONRAD has supported development of an important model of the heterosexual transmission of HIV with the simian retrovirus, SIV, in rhesus macaque monkeys. These studies have concluded that SIV<sup>mac</sup> is transmitted across the genital epithelia of male and female rhesus macaques, resulting in a long-term, persistent infection. This model is now being used in applied research to address specific questions concerning the effects of contraceptives on SIV transmission.

Currently, two projects are being funded: an examination of effects of progesterone implants on the heterosexual transmission of SIV; and the continued development of the SIV model, including research on physiology of viral infection, possible mucosal resistance, and the effects of a regimen of nonoxynol-9 (N-9) on SIV transmission.

## Recommendation

11. CONRAD's continuing investment in the simian model of HIV infection should be focused on the effects of contraceptive methods and virucides on SIV infection.

### *2.3.2 The Screening of Spermicidal and Microbicidal Candidates*

Spermicidal/Microbicidal-Virucidal Testing. CONRAD/NICHD has provided intramural funding for the screening of spermicidal products, and support to SRI for the development of assays to test these products for their virucidal and microbicidal activity. The aim has been to identify and develop topical products that can prevent conception and STD infection. The screening program is an important service that has been offered to a wide variety of investigators and institutions/agencies. CONRAD has screened close to 200 compounds and currently has several candidates that are both spermicidal and microbicidal, and will soon proceed to toxicology (vaginal irritation) testing. (See Section 2.2.3 on chemical barriers for additional discussion of the CONRAD screening program.)

Additionally, CONRAD/NIAID is investigating the in-vivo effects of N9 and benzalkonium chloride (BZK) on chlamydial infection in the pigtail macaque. The findings have shown that a single dose of 45 mg N-9 does not affect lactobacillus and partially protects against chlamydial infection. BZK once a day for two days decreases lactobacillus and has not yet been evaluated for STD protection.

Spermicidal/microbicidal-virucidal testing offers a potentially important service to the reproductive health community at large; to CONRAD's credit, it represents an open collaborative effort. By

several accounts, however, the screening program could benefit from increased efforts at coordination and streamlining. The recent departure of a senior intramural investigator, Dr Gustavo Doncel, represents an unfortunate interruption to ongoing activities, and may affect the long-term quality of this research. On the other hand, the new concerted strategy coordinated through TOPCAD offers promise for accelerating progress in this area.

In light of Dr Doncel's distance from the project, and the expansion of research efforts through TOPCAD, product development efforts will benefit from centralized oversight and planning, and monitored coordination of the various activities carried out by TOPCAD, SRI, EVMS and possibly, in Latin America. Without a concerted effort and commitment, candidate compounds may unnecessarily languish in early development stages.

## Recommendations

12. CONRAD should review whether Dr Doncel's supervision of the laboratory by fax, telephone and periodic visits is effective, or whether an interim appointment (or other such alternative) would significantly accelerate or improve work in this area.
13. **CONRAD should prepare a strategic, coordinated plan for rapid advancement of spermicidal/virucidal candidates through toxicity, to evaluations in the simian model, and to human testing.**

Given the apparent widespread prevalence of reproductive tract infections (RTIs) other than HIV throughout the world, but especially in developing countries, and the fact that concomitant RTIs are a risk factor for HIV transmission, the addition of anti-chlamydial and anti-gonococcal screening efforts through the TOPCAD program is a welcome development; increased attention to screening of RTI's other than HIV is encouraged.

### *2.3.3 Epidemiological and Behavioral Factors Affecting Transmission of HIV/STD's*

This programmatic area addresses important questions concerning the natural history of HIV infection, health-seeking and other behaviors (including contraceptive use) among HIV-infected persons, and factors affecting heterosexual HIV transmission among discordant couples. The majority of this research is supported through CDC funding, and managed by a CONRAD investigator based in Atlanta; one study in Zimbabwe receives direct funding from CONRAD/AID/W resources.

Natural History of STD infection in HIV Positive Women. A major, inter-disciplinary study at SUNY is following a cohort of HIV-infected women, and investigating the impact of HIV-associated immunocompromise on the course of pelvic inflammatory disease and reproductive tract infections. The project has been extremely productive to date, and recent reports characterize the effects of HIV on several reproductive illnesses, including cervical cancer and herpes virus. Other recent findings underscore the significant role of Ob-Gyns as the health-providers with the greatest access to infected women at the time of HIV diagnosis.

The Effects of Contraception and Vaginal Preparations on HIV/STD Transmission. A current CONRAD/CDC study is designed to investigate whether use of steroid contraceptives alters women's susceptibility to HIV transmission; the study takes place among a heterosexual population in Northern Thailand. CONRAD/AID/W is also funding a study designed to investigate the relationship between the use of intravaginal preparations that cause dryness on the vaginal mucosa and flora, and HIV transmission in 100 Zimbabwean women.

Population studies of risk factors for HIV/STD transmission are notoriously problematic, given the large sample sizes required, the necessity for prospective designs, and the substantial number of likely confounders. They also pose inherent dilemmas for investigators, as motivation of study volunteers is necessary to encourage valid reporting of intimate behaviors, yet such close involvement may alter subject behavior.

In the case of the Zimbabwean study, additional problems are evident: for example, the probability of sero-conversion in this population over the life of the study does not appear to have been calculated, and thereby the power of the study to evaluate risk factors for sero-conversion is questioned; the cross-sectional portion of the study suffers from the obvious limitation of recall bias, given the seriousness of the disease being investigated. Strategies for maximizing subject compliance, especially with regard to accurate prospective reporting of sexual activity, are not evident.

Behavioral Determinants of Sexual and Reproductive Health Decision Making. CONRAD/CDC is funding two studies to address behavioral determinants of HIV infection and determinants of reproductive health decision-making in the U.S. While much of the above CDC-funded research is of significant public health importance, and the majority of it appears to be well executed, some projects warrant greater technical oversight. The pass-through arrangements facilitating this research are not optimal. Relying on one CONRAD staff member to oversee such a large portfolio that is outside CONRAD's area of comparative expertise, limits the extent of technical oversight available, and may obscure appropriate lines of advice and accountability.

## **Recommendation**

- 14. Epidemiologic and behavioral research are not areas where CONRAD possesses the comparative advantages that it has in other areas of research in which it is involved. Either CDC-funding for these projects should provide for additional CONRAD professional staff in epidemiology and/or social science, or CDC-funded projects of this nature may be better handled by another agency.**



## **3 COLLABORATION AND COOPERATION**

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### **3.1 Overview**

CONRAD is to be commended for the excellent job it has done in communicating and collaborating with other agencies, including CDC, FDA, FHI, HRP/WHO, Mellon and Rockefeller Foundations, NIH, and the Population Council. CONRAD's collaborative activities have elicited consistent high praise. Manifestations of CONRAD's cooperative orientation include:

- the breadth of current funding sources (CDC, NICHD, Mellon), and expectations for additional sources
- provision of technical services to inter-agency interests (e.g. spermicidal and microbical screening, consultation on formulation problems with HRP002)
- the forum provided by the TAC for many participating agencies to collaborate on technical issues
- involvement in the interagency working group on microbicides
- the recent Bellagio and Institute of Medicine initiatives with the private sector
- funding of US centers participating in WHO multi-center trials

### **3.2 Programmatic Collaborations with other CAs**

Substantial collaboration with FHI has recently allowed the development of a cooperative style on both technical and programmatic aspects that is highly praised by all involved. Early difficulties in collaboration with FHI have been overcome. CONRAD has successfully collaborated with the Population Council on several research projects. While there have been some problems during the last year, the current interagency working group on microbicides is providing a forum for improved cooperation. Other fora for cooperative work with the Population Council are encouraged.

The additional funding and collaborations that CONRAD has had from other agencies of the federal government and private foundations exemplifies the ability of the organization to respond to and cooperate with the reproductive health field as a whole.

### **3.3 Collaboration with LDC Institutions**

CONRAD has numerous active collaborations with research centers in developing countries. These include:

- Institute of Primate Research (IPR), Nairobi, Kenya
- Instituto Chileno de Medicina Reproductiva (ICMER), Santiago, Chile
- National Institute of Immunology, under the Department of Biotechnology (DBT), Ministry of Science and Technology, New Delhi, India
- Indian Council for Medical Research (ICMR), New Delhi, India
- Instituto Nacional de la Nutrición Salvador Zubiran (INNSZ), Mexico City, Mexico
- Research Institute for Health Sciences (RIHES), Chiang Mai, Thailand

These centers provide opportunities to increase the solicitation of project proposals from LDC investigators, identify potential LDC members of the TAC, and provide advice to CONRAD regarding the "appropriateness" of new contraceptive leads for the developing country market.

## **Recommendation**

15. CONRAD should capitalize on existing developing country centers to increase the level of engagement and participation of LDC scientists (and others) in the CONRAD program.

### **3.4 Impact of the NIH and CDC Contracts on CONRAD's Contraceptive Research**

Concern about the interrelations between methods of fertility regulation and HIV/STDs transmission is widely reflected in the CONRAD program. Special attention has been given to the development of women-controlled methods that are intended to protect against pregnancy and STDs and AIDs. The animal model developed for the study of SIV transmission can now be used to evaluate the possible interaction between systemic, mechanical and chemical contraception and susceptibility to HIV and other sexually transmitted pathogens. Likewise, research on the mechanisms of HIV transmission and on the physiology of HIV in the human genital tract open new avenues for development of products offering virucidal protection.

As such, the addition of CDC and NIH funding for HIV/AIDS research appears, in the majority, to have provided complementary intellectual resources to CONRAD, and in-house expertise on the emerging nexus between contraception and HIV/STD transmission. Given the public need for products that will allow selective or combined protection to conception and disease, CONRAD's integrated portfolio is well positioned to advance the field.

Two concerns are worthy of mention. First, at the present time it appears that methods providing substantial protection from conception and disease are likely to be coitus-specific products, requiring frequent administration. Given that substantial need for long-acting, non-coital dependent methods will also continue for the foreseeable future, development of these latter methods should not be eclipsed by the program's commitment to HIV/STD protection. Second, as mentioned in Section 2.2.3 above, current pass-through mechanisms for funding significant epidemiological and behavioral research on HIV are not optimal. While much of the work is of high-quality, some projects warrant greater technical oversight. As CONRAD's superior technical capabilities lie in other areas of research, appropriate management of these epidemiologic and behavioral projects may serve as a distraction from CONRAD's mission. On the other hand, CONRAD is well-positioned to undertake intramural pharmacokinetic studies on the interaction between systemic contraceptive agents and anti-HIV drugs such as AZT. It is unlikely that other research centers have CONRAD's clinical research capacity for such research.

## 4 MISSION AND PLANNING

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### 4.1 Strategic Planning

CONRAD's strategic planning needs include:

- Identification of means to increase the number and quality of basic research leads.
- Allocation of portions of funding for investment in different leads.
- Ensuring that research is informed by an LDC perspective.
- Planning for future changes in the availability of funds.
- Identification of pro-active strategies to maximize program effectiveness in the coming years.

Contraceptive development is largely driven by the availability of new leads. The present reality of a near exhaustion of leads underscores the need for concerted strategies for identifying and nurturing any areas of untapped potential, and weighing the relative value of opportunities that appear feasible and useful, even if they do not constitute a dramatic breakthrough in fertility regulation. The relative value of given leads will include evaluation of the product's market potential in developing countries.

At present, the process by which these, and other strategic decisions are taken in CONRAD is not transparent. It appears that strategic planning and policy is occurring on a short-term basis, and is principally in the hands of CONRAD's director and the cognizant technical officer (CTO), with some input from the TAC and the senior professional staff at CONRAD and USAID/W.

#### *4.1.1 Role of USAID*

Given the close proximity of USAID and CONRAD's Rosslyn offices, there is ample opportunity for frequent consultation between the CTO, other USAID/W staff, and CONRAD's director and/or staff. The proximity has many advantages, but by fostering an ad hoc planning style, it may obscure the value of establishing a more systematic policy-making unit for CONRAD.

#### *4.1.2 Role of the TAC*

The 1989 midterm evaluation and the latest five-year cooperative agreement both specifically recommended that the TAC, in addition to its role in peer review, be used to advise CONRAD in developing overall and specific R&D strategies, and establishing overall program priorities. At present, as evidenced from the minutes of TAC meetings, and consultations with those attending TAC meetings, the TAC is not fulfilling this role.

## Recommendation

16. **There is a strong need for CONRAD to establish a policy unit/entity that would provide "board-like" functions, including the development of long-term strategic plans, oversight of TAC appointments, and annual review of the program. LDC participation in the unit is recommended.**

There are numerous possible configurations for such a unit. The following example is meant to be illustrative. A possible configuration could include a chairperson of the TAC, CONRAD's director, the CTO, and two or three senior scientific advisors. Such a unit could meet semi-annually, a month or two prior to the TAC meeting, ensuring that strategic decisions needing TAC review were adequately prepared prior to the TAC meeting. To ensure impartiality by the policy unit, it might be worthwhile to require that external scientific advisors are neither directly engaged with CONRAD-funded activities, nor members of other USAID CAs. CONRAD and the CTO may wish to review various options in consultation with a short-term management consultant (see Recommendation number 31).

### 4.2 Solicitation of Research

The success of CONRAD is highly dependent on identifying promising research leads for contraception. To date, CONRAD has not been able to elicit as much response for project ideas as had been hoped at the outset of the program. Similar experiences by other agencies suggest a paucity of available ideas and opportunities arising from the basic research sector.

Given that reality, strategies for solicitation must be innovative, polished, and far-reaching, and maximum use must be made of CONRAD's professional staff and the TAC, in this regard. A similar recommendation was made in the 1989 midterm evaluation. Significant improvements have been made in this area, and several announcements and RFAs have been issued. Further efforts are needed.

The reach of the solicitation process can be increased further. For example, use could be made of foreign national or regional reproductive health and/or gynecology and obstetrics societies' newsletters, bulletins or specialized journals, which have a much larger readership in developing countries than even the widely circulating international journals.

All solicitation strategies rely upon CONRAD's institutional visibility, domestically and internationally. The external image of CONRAD is largely associated with that of its director, Dr Gabelnick. While that image is extremely positive, the program will benefit if it takes concerted steps to further expand its "institutional" visibility beyond that of the director.

## Recommendations

17. Workshops sponsored by CONRAD should include invitations to professionals who may not currently be engaged in contraceptive research, but who may be encouraged, through participation at the workshop, to develop project proposals investigating contraceptive applications of their work.
18. **Increased outreach to the international scientific community by professional staff is encouraged. Advertisement in foreign national journals should be explored, and increased efforts should be made to solicit research ideas through existing associations with developing country scientists (e.g. through the Mellon Centers).**
19. Increased institutional presence at professional meetings, and establishing a CONRAD "booth" at large meetings should be considered.
20. The CONRAD brochure should be reviewed and improved by an appropriately qualified consultant.

### 4.3 Selection of Projects

#### 4.3.1 *Selection of Extramural Projects*

Review of extramural subprojects frequently begins with telephone contact by a prospective investigator, or submission of a brief preliminary proposal. Preliminary proposals are reviewed by the CONRAD staff and discussed at staff meetings. Those which appear promising are invited to submit a full project proposal which is initially reviewed by CONRAD staff and later submitted to the TAC for review. Promising proposals that require modifications or further development, are frequently offered and receive assistance from CONRAD staff. There is no indication that the TAC plays a significant role in generating proposals, with the exception of projects carried out at centers where members of the TAC are affiliated.

After the screening of preliminary proposals described above, which may have included modifications recommended by CONRAD staff, extramural proposals are reviewed semi-annually by the TAC. The TAC may approve without modifications, suggest changes before approval, request a pilot project to test feasibility before a formal review, or may reject proposals. The average time interval from initial staff review of projects to eventual funding of full proposals for projects funded during the latter half of 1994 was six months. This is extremely rapid, and CONRAD is commended for rapid review and development of projects.

#### 4.3.2 *Selection of Intramural Projects*

Intramural proposals may be generated by the CRU or research laboratory in Norfolk, from any senior CONRAD researcher, or develop as part of a larger multi-center study. They are reviewed by the director and senior researchers at Rosslyn and Norfolk, and do not require prior approval by

the TAC if the budget is below US \$25,000. They are, however, subsequently reported to the TAC during semi-annual reviews.

## **Recommendations**

21. Broader TAC and staff collaboration in generating and developing good proposals from promising ideas (extramural and intramural) should be encouraged.
22. The establishment of clear criteria to judge the appropriateness to LDC needs is encouraged.
23. The experience and closer relations with clients of the Norfolk staff can provide significant input to the program. The director and senior staff at the CRU should be encouraged to participate more actively in generating subprojects, reviewing proposals and developing general strategies for the program.

## **4.4 Monitoring of Projects**

### *4.4.1 Project Reporting to CONRAD*

CONRAD requires semi-annual progress reports from all intramural and extramural projects. Compliance with reporting appears excellent. A product development specialist has recently joined the CONRAD staff. Among other things, he will develop improved workplans and "tracking" of progress in individual product lines.

### *4.4.2 Multi-center Trials*

The current system for monitoring multi-center clinical trials from the Rosslyn office appears highly effective. Oversight provided by Rosslyn staff is efficient, and coordination of data management with FHI is working smoothly.

### *4.4.3 Reporting to USAID*

Semi-annual reporting to USAID encompasses the detailed project-by-project reports, and a brief workplan for the coming interval. The reports would be strengthened by less detail, and greater attention to a summary of the program's overall progress, and description of strategic plans for the coming year.

## **Recommendations**

24. CONRAD should consider the possibility of producing only an annual report to USAID, which would not include detailed project-by-project reviews, but would provide an overarching annual review of CONRAD's progress and a strategic plan of work for the coming year.
25. CONRAD should investigate developing a system of research lead "champions" among staff professionals (and possibly in partnership with individual TAC members), both to increase staff and TAC accountability for given leads, and to accelerate progress on individual lines of research.





## 5 TECHNICAL ADVISORY COMMITTEE

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### 5.1 Composition

The current TAC membership includes 12 persons (eight men and four women), who provide good representation from relevant technical fields. Additional technical advice is solicited through working groups. Other persons participating in TAC meetings include representatives of cooperating agencies, USAID, WHO, NIH, CDC, CONRAD staff, and guests. Meetings can include more than 40 persons, yet there is little apparent representation from developing countries. The 1989 midterm evaluation specifically recommended that LDC members be included in the TAC.

At present there is no formal procedure for selection of new members, e.g. a designated nominating committee that searches for appropriate candidates and proposes names for board approval. In addition, the TAC does not have terms of service (i.e. term limits) for its members.

### 5.2 Mandate

TAC meetings are principally used for peer review of proposals and active research. As mentioned earlier, there is little evidence that the TAC is systematically engaged in strategic planning. The meetings are too large for effective use of this body for strategic planning. The evaluation team has recommended establishment of a separate policy unit/entity to this effect (see Recommendation 16), and the TAC mandate can be changed accordingly.

### Recommendations

26. The TAC mandate should be modified to include review of policy issues brought to it by the "policy unit/entity" described in Recommendation 16. The agenda should be modified to allow time for such policy review.
27. **There is a clear need to increase representation from developing countries, both in the TAC, and in the recommended "policy unit".**
28. A formal procedure for selection of new TAC members should be established.
29. There is a need to review the issue of term limits, and the evaluation team recommends establishment of three-year (once-renewable) limits for TAC members.



## **6 FINANCIAL MANAGEMENT**

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### **6.1 Budgeting**

CONRAD has responded to USAID's mandate regarding the budget allocation between intramural and extramural research. As Chart 1 (Appendix D) shows, taking account of only USAID funds, extramural projects represented 53.7 percent of total expenditures for the period 6/1/92 - 11/30/94 in contrast to 2.6 percent for intramural research (excluding salaries in each case). When USAID, CDC and NIH funds are included, the percentages for the same period are 64.4 percent for extramural and 1.9 percent for intramural (these figures exclude salaries for intramural projects) as shown in Chart 2 (Appendix E). It is also the judgement of the evaluation team that the budget breakdown among line items is very reasonable.

CONRAD has clear procedures for development, review and approval of budgets for research. CONRAD's guidelines for research applications spell out requirements for line item budgets which must be submitted with each proposal. Multi-year projects must have a separate annual budget for each year. Indirect costs are limited to 10 percent of direct costs. Subprojects are administered on a cost reimbursement basis.

When a proposed research subproject budget is received by CONRAD, it is reviewed by professional staff, usually by the TAC, and subsequently by the CONRAD administrator for fiscal affairs before being approved by the CONRAD director.

### **6.2 Financial Reporting**

CONRAD has excellent procedures for monitoring and reporting on expenditures. CONRAD has developed a system to track actual expenditures in comparison with approved budgets. Subproject financial reports are examined by the accounting staff to assure that budgets are not exceeded and by technical staff to assess correlation between progress and expenditures. CONRAD's reports to USAID have virtually always been timely and complete.



## **7 STAFFING, ORGANIZATION AND MANAGEMENT**

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### **7.1 Staffing**

CONRAD's staff is competent and hardworking. There are plans for modest staff additions in Rosslyn, notably to increase the capacity for managing clinical trials activity. See Chart 3 (Appendix F) for the organization of CONRAD staff in Rosslyn.

#### **Recommendation**

30. USAID should approve CONRAD's plans for modest additions to staff in Rosslyn.

### **7.2 Organization and Management**

There are management issues which need to be addressed if CONRAD is to realize its full potential. These issues are: management structure, decision making, delegation of authority, information sharing and communication, management styles, professional development, strategic planning and institutional visibility. A management consultant should be engaged to assist CONRAD (and USAID) to improve relevant management systems and processes. The consultant should be selected from a short list by CONRAD's director, CONRAD's professional staff and relevant staff in USAID. The consultant should make short follow-up consultations after three months, six months and one year to assess progress.

CONRAD may not be taking full advantage of the capabilities of the intramural research staff in Norfolk. The evaluation team found that the quality of the Norfolk CRU is excellent and believes that it could make greater contributions to the deliberations of staff in Rosslyn.

There is a need to clarify and make more systematic the relationship between CONRAD and USAID, particularly with respect to strategic planning and decision making.

CONRAD currently does not have an entity with "board-like" responsibilities for ensuring the development of policies and strategic plans, periodically reviewing the achievement of plans, and appointing members of the TAC. (See Recommendation 16.)

#### **Recommendations**

31. **A management consultant should be contracted to assist CONRAD and USAID to address the management issues identified above.**
32. CONRAD should take better advantage of the capability which exists in Norfolk by, for example, having the chief of the CRU participate in CONRAD staff meetings.



## **8      FACILITIES**

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CONRAD labs and office facilities are generally adequate. Additional office space may be needed if there are staff additions in Rosslyn. Ideally, the office space should be on one floor.





## 9 FUTURE DIRECTIONS AND RECOMMENDATIONS

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### 9.1 Continuation

Since its 1989 midterm evaluation the CONRAD program has come back on track. The present portfolio is focused on near-term leads, and is principally composed of extramural projects. The current director is to be commended for assembling a first-rate professional staff, and for effectively coordinating activities in both Rosslyn and at the CRU in Norfolk. Given these strengths, evident in recent accomplishments in both product development and fundamental HIV research, the evaluation team strongly recommends that the CONRAD program be continued for an additional ten years, with appropriate review at five years.

CONRAD's effectiveness is enhanced by its relatively small size, its proximity to the Norfolk CRU, and by systems that allow for rapid coordination of activities with other US-based, international, and LDC institutions. Given these unique strengths, the team sees no clear advantage to merging CONRAD with any of the other CAs.

For similar reasons the team recommends that the continuation of CONRAD not be competed. First, it is very unlikely that the quality and commitment of the director and the professional staff, or the responsiveness of the EVMS CRU could be matched elsewhere. Second, achievement of CONRAD's mission is highly dependent on effective cooperative linkages with other CAs, federal agencies, international agencies and foundations. As CONRAD has performed exceptionally well in this regard, it is unlikely that another institution could offer comparable advantages.

### Recommendation

- 33. The CONRAD program should be continued as an independent CA for an additional ten years, with appropriate review at five years. The continuation should not be competed.**

### 9.2 Improved Mechanisms for Policy and Planning

The CONRAD program can be improved by attention to several important issues. The evaluation team strongly recommends that CONRAD establish a "policy unit" or entity that can provide "board-like" functions, including the development of long-term strategic plans, oversight of TAC appointments, and annual review of the program. This entity should be small (four to six members), and include senior scientific advisors without direct involvement with CONRAD-funded research. LDC participation is strongly recommended. The evaluation team envisages the entity meeting semi-annually, and bringing policy issues to TAC for broader debate as needed.

### 9.3 Ensuring Program Responsiveness to LDC Needs

It is widely agreed that LDC needs for contraception are hard to define. They are certainly variable, and may well be changing in response to social development. As such, ensuring CONRAD's responsiveness to LDC needs cannot be met by any single strategy, but must be addressed by several strategies at once. LDC participation in the TAC is essential, and representation in the "policy unit" is strongly recommended. Systems for greater outreach through LDC collaborating centers should be explored, and participation at upcoming international fora on this issues is encouraged.

### 9.4 Relaxing the Product Development Mandate

The USAID mandate for rapid product development should be relaxed to allow increased opportunities for exploration of long-term leads. The current mandate for four to five "products" per cycle may actually be narrowing the likelihood of achieving the overall objective of developing new and improved contraceptive methods for LDCs. The emphasis on rapid product development, if too extreme, may lead to acceleration of sub-optimal short-term leads, especially mechanical leads that do not require pharmacokinetic testing, at the expense of more innovative, and important, long-term leads. To this end, the team commends CONRAD for expanding their funding sources in order to facilitate a greater range of activities.

### 9.5 Streamlining and Focusing the HIV/AIDS Portfolio

There is a need for CONRAD to develop a strategic, coordinated plan for rapid advancement of products through toxicology, to evaluation in the simian model, and to human testing. While the epidemiologic and behavioral HIV research funded by CDC provides some intellectual complementarity to CONRAD's interests, it is not optimally suited to CONRAD's mission and technical expertise; epidemiologic and social science projects of this nature may be better handled at CDC. On the other hand, the CONRAD intramural capacity to carry out pharmacokinetics studies could be better used to investigate interactions between systemic contraceptive agents and anti-HIV drugs.

### 9.6 Priorities in the Event of Reduced Funding

The evaluation team strongly recommends sustained or increased funding to CONRAD. Nonetheless, in the event that reductions prove inevitable, the team recommends the following:

- Attention to female mechanical barriers should continue only in the event that a new method offers significant improvements over existing products.
- Attention to chemical barriers should be increased.
- Immunocontraceptive research should be critically reviewed with attention to scaling back all but the most promising leads.
- Testing of **existing** male systemic agents should be critically reviewed, with increased attention given to development of **new**, and better steroid formulations.

- Local male methods should continue to be explored.
- Research on methods for lactating women should be given high priority.
- Basic research by Anderson and Marx should be scaled back, but the applied models should definitely be maintained.
- Core CONRAD-funded exploratory research on vaginal drying agents should be critically reviewed by external consultants.

In future, the CONRAD "policy unit" will be able to provide annual recommendations regarding areas of research to be accelerated, scaled back, or eliminated.